Remarks

Claims 1-36, 56, 58-80, 97, 101, 108, 112, 120 and 121 are currently pending.

Applicants request that the Examiner update the listing of claims on the Office Action Summary Sheet. Note that claim 57 was previously canceled, and Claims 120 and 121 were previously added. The Examiner has acknowledged, however, the addition of Claims 120 and 121 on page 2, and the allowance of Claim 120 on page 16 of the Office Action mailed on September 27, 2005.

Applicants thank the Examiner for rejoining method of use Claims 101, 106-108 and 112.

In order to expedite the current application to allowance, Applicants have amended claim 108 to direct the claim to the treatment of Obesity. Applicants herein cancel Claims 106, 107 and 112, and reserve the right to pursue claims covering methods of use for other than Obesity in one or more continuation applications.

Applicants have also amended Claims 1 and 56 to delete recitation of prodrugs and solvates. Claims 2-36, 58-80, 97, 101, and 121 are amended to delete recitation of solvates.

The Examiner has made rejections of various claims under 35 USC 112, 2nd paragraph, objecting to the use of the term "prodrug." Applicants point out that rejected dependent Claims 2-36, 58-80, 97, 101, and 106-108, do not encompass prodrugs. Applicants also point out that Claim 121 is not dependent upon claim 1. With respect to these claims, Applicants submit that the rejections are improper.

Claims 1 and 56 are each amended to delete the term prodrug. It is submitted that the rejections with respect to the term "prodrugs" have been obviated.

The Examiner has rejected claims under 35 USC 112, 1st paragraph, for lack of enablement. The Examiner asserts that the specification does not teach how to make solvates or hydrates.

Applicants have deleted recitation of solvates in the claims.

With regard to hydrates, the Examiner argues that the enablement is insufficient because there is no Example of a hydrate, and hydrate formation is unpredictable.

Applicants point out that hydrates are generally formed during a recrystallization process and not directly from a reaction mixture or isolation process, as disclosed in the Examples. Those of skill in the art know how to generate a crystalline form from a solid form and then produce a hydrate from such crystalline material. The preparation of hydrates of organic compounds is routine in the art as evidenced in *Polymorphism in Pharmaceutical Solids*, ed. Harry G. Brittan, Vol. 95, Marcel Dekker, Inc., New York, 1999 pg. 202-205, enclosed. Applicants are not required to provide detailed descriptions of processes which are well known and are common practice among pharmaceutical chemists. Moreover, because preparation of hydrates is routine in the art, no undue experimentation would be required to practice the invention.

Applicants note that controlling precedent requires that the US PTO accept the objective truth of Applicants' teachings of enablement unless there is a reason to doubt these teachings. Applicants respectfully submit that there is no reason to doubt the objective truth of the statements contained within the Specification upon which Applicants rely for enabling support.

It is submitted that the rejection has been overcome.

The Examiner has rejected claims under 35 USC 112, 1st paragraph, as non-enabling for the use of the compounds for indications other than obesity. (The Examiner has acknowledged on page 10, line 14 of the office action that the specification is enabled for the treatment of obesity). Applicants respectfully submit that the amendment to Claims 101 and 108 and the cancellation of Claims 106, 107 and 112 render this rejection moot.

Although Applicants have limited the current method claims to the treatment of obesity, Applicants reserve the right to pursue the other indications in one or more separate continuation applications. The cancellation of Claims 106, 107 and 112, and

the amendment of Claims 101 and 108 should not be construed as an admission by the Applicant of non-enablement for indications other than obesity.

It is submitted that the rejection has been overcome.

Based on the amendments to the Claims and the arguments provided above, Applicants respectfully submit that the claims are in condition for allowance.

A Petition for Extension of Time – three months, is enclosed. If any required fees are missing or deficient, please charge our deposit account number 16-1445.

Respectfully Submitted:

Date: Mar 23, 2006

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the crystal free to grow at the opposite pole. Since it is bound at the slow growing NH_{3+} end of the polar axis, it does not interfere with the fast growing CO_{2-} end.

J. Grinding

Polymorphic transformations have been observed to occur on grinding of certain materials, such as sulfathiazole, barbital, phenylbutazone, cephalexin, chloramphenicol palmitate, indomethacin, and chlorpropamide. Byrn [46] has stated that polymorphic transformations in the solid state require the three steps of (a) molecular loosening (nucleation by separation from the lattice), (b) solid solution formation, and (c) separation of the product (crystallization of the new phase). Depending on the material and the conditions employed, grinding can result in conversion to an amorphous substance. With the exercise of care, different polymorphic forms can be obtained. Otsuka et al. [57] showed that metastable Forms B and C of chloramphenicol palmitate were transformed into stable Form A upon grinding at room temperature. Indomethacin was transformed into a noncrystalline solid during grinding at 4°C, and into metastable Form A by grinding at 30°C. Caffeine Form II is converted into Form I with grinding, and a 95% phase conversion was obtained following 60 hours of grinding time [38].

II. Methods Employed To Obtain Hydrate Forms

Pharmaceutical solids may come into contact with water during processing steps, such as crystallization, lyophilization, wet granulation, aqueous film-coating, or spray-drying. Moreover, they may be exposed to water during storage in an atmosphere containing water vapor, or in a dosage form consisting of materials that contain water (e.g., excipients) and are capable of transferring it to other ingredients. Water may be adsorbed onto the solid surface and/or may be absorbed in the bulk solid structure. When water is incorporated into the crystal lattice of the compound in stoichiometric proportions, the molecular adduct or adducts formed are referred to as hydrates [58]. More than 90 hydrates

are described in various USP monographs. Hydrates can be prepared by recrystallization from water or from mixed aqueous solvents. They can also result, in some instances, from exposure of crystal solvates (such as methanolates or ethanolates) to an atmosphere containing water vapor.

Crystalline substances often form with water molecules located at specific sites in the crystal lattice, which are held in coordination complexes around lattice cations. This type of water is denoted as water of crystallization and is common for inorganic compounds. For example, nickel sulfate forms a well-defined hexahydrate, where the waters of hydration are bound directly to the Ni(II) ion. Extraneous inclusion of water molecules can occur if a coprecipitated cation carries solvation molecules with it. Water also can be incorporated into random pockets as a result of physical entrapment of the mother liquor. Well-defined multiple hydrate species can also form with organic molecules. For example, raffinose forms a pentahydrate.

Although most hydrates exhibit a whole-number-ratio stoichiometry, an unusual case is the metastable hydrate of caffeine, which contains only 0.8 moles of water per mole of caffeine. Only in a saturated water vapor atmosphere will additional amounts of water be adsorbed at the surface of the 4/5-hydrate to yield a 5/6 hydrate [59].

In some instances, a compound of a given hydration state may crystallize in more than one form, so that the hydrates themselves exhibit polymorphism. One such example is nitrofurantoin, which forms two monohydrates that have distinctly different temperatures and enthalpies of dehydration. The monohydrates have quite different packing arrangements, with Form I possessing a layer structure and Form II exhibiting a herringbone motif. The included water molecules play a major role in stabilizing the crystal structures. Whereas water molecules are contained in isolated cavities in Form II, in Form I they are located in continuous channels, and this apparently facilitates the escape of water when these crystals are heated [60].

Another example of hydrate polymorphism is amiloride hydrochloride [61], which can be obtained in two polymorphic dihydrate forms. These forms are indistinguishable by techniques other than x-ray powder diffraction.

It is interesting that scopolamine hydrobromide has been reported

to exist as the anhydrous form, a "hemihydrate," a sesquihydrate, and a trihydrate [62], while the unit cell parameters and the molecular geometry of these are all the same as those of the hemihydrate. This finding suggests that the "hemihydrate" is actually a partially desolvated sesquihydrate.

Ouabaine is another example of a compound that exhibits many different hydration levels, the most hydrated form being stable at the lowest temperature. Thus the nonahydrate phase of ouabaine is obtained from water at 0–15°C, the octahydrate phase at 15–28°C, and the dihydrate phase at 28–90°C. In addition, ouabaine phases corresponding to 4.5 H_2O, 4 H_2O, and 3 H_2O may be obtained from mixtures of water with other solvents. The anhydrous phase of ouabaine anhydrate is crystallized from ethanol at high temperatures [63].

Typically, hydrates are obtained by recrystallization from water. For example, trazodone hydrochloride tetrahydrate was prepared by dissolving the anhydrate in hot distilled water, allowing the solution to remain at room temperature overnight, and storing the collected crystals at 75% relative humidity and 25°C until they reached constant weight [64].

Hydrates can sometimes be obtained by simply suspending the anhydrous material in water, whereupon a form of Ostwald ripening occurs. For instance, aqueous suspensions of anhydrous metronidazole benzoate are metastable, and storage at temperatures lower then 38°C leads to monohydrate formation accompanied by crystal growth [65]. Sorbitol provides another example of this behavior, where slow cooling of a saturated aqueous solution yields long thin needles of sorbitol hydrate [66]. When suspended in water, anhydrous carbamazepine is transformed to carbamazepine dihydrate [67]. In other instances, hydrates can be obtained from mixed solvent systems. Acemetacin monohydrate can be obtained by slow evaporation from a mixture of acetone and water at room temperature [68].

Simply exposing an anhydrous powder to high relative humidity can often lead to formation of a hydrate. On exposure to a relative humidity of 100%, dexmedetomidine hydrochloride is converted to a monohydrate [69]. Droloxifene citrate is an example of a compound that is not very hygroscopic and yet forms a hydrate. Only after storage of the anhydrous form at 85% relative humidity does some sorption of

water occur. The monohydrate phase can be formed by exposing the anhydrous form to 98% relative humidity for ten days at 24°C [70].

III. Methods Employed To Obtain Solvate Forms

Often, when solvents are employed in the purification of new drug substances by recrystallization, it is observed that the isolated crystals include solvent molecules, either entrapped within empty spaces in the lattice or interacting via hydrogen bonding or van der Waals force with molecules constituting the crystal lattice. Solvent molecules also can be found in close association with metal ions, completing the coordination sphere of the metal atom. Coordinated solvent molecules are considered as part of the crystallized molecule. A crystal with large empty channels or cavities is not stable because of packing demands. The size and chemical environment of the cavity or channel determine what kind of solvent molecule can be included in the structure and what kind of interaction occurs between solvent and structure.

Depending on the nature of molecular packing arrangements, it may happen that the inclusion of solvent is necessary to build a stable crystal structure. van Geerestein et al. [71] found during numerous crystallization attempts of 11β-[4-(dimethylamino)phenyl]-17β-hydroxy-17α-(I-propynyl) estra-4,9-diene-3-one] that crystals were only obtainable in the presence of *n*-butyl acetate or *n*-propyl acetate. The crystal structure of the compound crystallized from *n*-butyl acetate/methylcyclohexane was solved, and one solvent molecule was found in the crystal structure that showed no strong interactions with the rest of the structure. Apparently, this solvent molecule was necessary to fill empty space resulting after the molecular packing. Solvates in which the solvent fills empty space are generally nonstoichiometric, such as the nonstoichiometric solvates formed by droloxifene citrate with acetonitrile, 2-propanol, ethanol, 1-propanol, and 1-butanol. Typically such solvates exhibit the same x-ray diffraction pattern as does the nonsolvated compound.

When solvent molecules increase the strength of the crystal lattice, they can affect the stability of the compound to solid-state decom-